IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:	:	
Curran; *et al.*	:	Art Unit: 1652
Serial No. 10/078,927	:	Examiner: David J. Steadman
Filed: February 19, 2002	:	Atty Docket: SJ-01-0032
For: Cyclin Dependent Kinase 5 Phosphorylation of Disabled 1 Protein	:	

Mail Stop Amendment
Commissioner for Patents
PO Box 1450
Alexandria, VA 22313-1450

DECLARATION UNDER 37 C.F.R. §1.132
By
Dr. Thomas Curran

Sir:

I, Thomas Curran, do hereby declare and say as follows:

1. I am skilled in the art of the field of the invention of the above-referenced application. I have a PhD from Imperial Cancer Research Fund Laboratories and University College London, UK. I have been engaged in the study of development neurobiology for 21 years. I have been a faculty member and the Chair of the Department of Developmental Neurobiology at St. Jude Children's Research Hospital since 1995. The department consists of 8 faculty members and more than 50 employees. I am a past president of the American Association for Cancer Research and currently serve on the National Cancer Institute Board of Scientific Advisors. I am the current editor of Developmental Brain Research.

2. I am a co-inventor of the above-referenced application.

3. At the time of filing of the present invention on February 19, 2002, a person of skill in the art was capable of easily determining the scope of proteins that were encompassed by the term "Cdk5". Cdk5 was distinguishable from other proteins, including other closely related proteins, such as Cdc2, Cdk2, Cdk4 and Cdk6. Unlike other cdks, Cdk5 kinase activity has been observed only in the adult brain. The expression and activity of Cdk5 increases as increasing numbers of cells exit the proliferative cycle, which is in contrast to the expression activity of cdc2 and cdk2. In contrast to other cell division cycle kinases to which it is closely related, cdk5 appears not to be expressed in dividing cells in the developing brain. Ckd5 is a serine/threnonine kinase which has approximately 60% structural identical to Cdc2 and Cdk2. (Tsai LH, Takahashi T, Caviness VS Jr, Harlow E., Activity and expression pattern of cyclin-dependent kinase 5 in the embryonic mouse nervous system., Development. 1993 Dec;119(4):1029-40) However, as shown in Exhibit A, Cdk5 from mouse, human and rat are virtually identical. Other publications identifying and describing Cdk5 existed in the art at the time the present invention was filed. They include:

A. Nikolic M, Dudek H, Kwon YT, Ramos YF, Tsai LH.
The cdk5/p35 kinase is essential for neurite outgrowth during neuronal differentiation.
Genes Dev. 1996 Apr 1;10(7):816-25.
PMID: 8846918 [PubMed - indexed for MEDLINE]

B. Songyang Z, Lu KP, Kwon YT, Tsai LH, Filhol O, Cochet C, Brickey DA, Soderling TR, Bartleson C, Graves DJ, DeMaggio AJ, Hoekstra MF, Blenis J, Hunter T, Cantley LC.
A structural basis for substrate specificities of protein Ser/Thr kinases: primary sequence preference of casein kinases I and II, NIMA, kinase, calmodulin-dependent kinase II, CDK5, and Erk1.
Mol Cell Biol. 1996 Nov;16(11):6486-93.
PMID: 8887677 [PubMed - indexed for MEDLINE]

C. Dhavan R, Tsai LH.
A decade of CDK5.
Nat Rev Mol Cell Biol. 2001 Oct;2(10):749-59. Review.
PMID: 11584302 [PubMed - indexed for MEDLINE]

4. At the time of filing of the present invention on February 19, 2002, a person of skill in the art was capable of easily recognizing a Dab1 protein and distinguishing it from other proteins, including the closely related Dab2 protein. Numerous publications identifying and describing Dab1 existed in the art. Howell et al., Mouse disabled (mDab1): a Src binding protein implicated in neuronal development. EMBO J. 1997 Jan 2;16(1):121-32 described mDab1 as a protein localized in the growing nerves of embryonic mice and as being tyrosine phosphorylated when the nervous system is developing, but not thereafter. This is in contrast to mDab2 which is widely expressed without any evidence of tyrosine phosphorylation or association with tyrosine-phosphorylated proteins. Howell et al., Dab1 tyrosine phosphorylation sites relay

positional signals during mouse brain development, Current Biology, Vol. 10:877-885 (2000) state that the identity between Dab1 and Dab2 in the PTB domain is 66%, in the DabH1 region is 73% and in the DabH2 region is 54%. However, as shown in Exhibit B, Dab1 amino acid sequences from mouse, rat and human are virtually identical throughout the entire protein. Other publications describing Dab1 and Dab2 include:

D. Xu XX, Yang W, Jackowski S, Rock CO.
Additions and Corrections to Cloning of a novel phosphoprotein regulated by colony-stimulating factor 1 shares a domain with the Drosophila disabled gene product.
J Biol Chem. 1996 May 31;271(22):13292. No abstract available.
PMID: 8663093 [PubMed - as supplied by publisher]

E. Xu XX, Yang W, Jackowski S, Rock CO.
Cloning of a novel phosphoprotein regulated by colony-stimulating factor 1 shares a domain with the Drosophila disabled gene product.
J Biol Chem. 1995 Jun 9;270(23):14184-91.
PMID: 7775479 [PubMed - indexed for MEDLINE]

F. Fulop V, Colitti CV, Genest D, Berkowitz RS, Yiu GK, Ng SW, Szepesi J, Mok SC.
DOC-2/hDab2, a candidate tumor suppressor gene involved in the development of gestational trophoblastic diseases.
Oncogene. 1998 Jul 30;17(4):419-24.
PMID: 9696034 [PubMed - indexed for MEDLINE]

G. Xu XX, Yi T, Tang B, Lambeth JD.
Disabled-2 (Dab2) is an SH3 domain-binding partner of Grb2.
Oncogene. 1998 Mar 26;16(12):1561-9.
PMID: 9569023 [PubMed - indexed for MEDLINE]

H. Sheldon M, Rice DS, D'Arcangelo G, Yoneshima H, Nakajima K, Mikoshiba K, Howell BW, Cooper JA, Goldowitz D, Curran T.
Scrambler and yotari disrupt the disabled gene and produce a reeler-like phenotype in mice.
Nature. 1997 Oct 16;389(6652):730-3.
PMID: 9338784 [PubMed - indexed for MEDLINE]

I. Howell BW, Hawkes R, Soriano P, Cooper JA.
Neuronal position in the developing brain is regulated by mouse disabled-1.
Nature. 1997 Oct 16;389(6652):733-7.
PMID: 9338785 [PubMed - indexed for MEDLINE]

J. Howell BW, Lanier LM, Frank R, Gertler FB, Cooper JA.
The disabled 1 phosphotyrosine-binding domain binds to the

internalization signals of transmembrane glycoproteins and to phospholipids.
Mol Cell Biol. 1999 Jul;19(7):5179-88.
PMID: 10373567 [PubMed - indexed for MEDLINE]

5. At the time of filing of the present invention on February 19, 2002, the term "Cdk5 serine kinase activity" was well understood and used extensively in the field. This statement refers to the ability of the enzyme (Cdk5) to transfer phosphate groups to specific serine residues present within a sequence of amino acid residues recognized by Cdk5.

6. Therefore at the time of filing of the present invention, a person of skill in the art was easily capable of distinguishing a Cdk5 or Dab1 protein from other proteins and could easily identify whether or not Cdk5 had serine kinase activity (e.g. was capable of phosphorylating serine).

7. Both Cdk5 and Dab1 proteins, especially the functional domains of each (the kinase domain of Cdk5 and the recognition sequence in Dab1) are highly conserved. Therefore, it is expected that the enzyme-substrate interaction is conserved among species that have a Cdk5 and Dab1 protein.

8. I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

T. Curran

Thomas Curran

April 22, 2005

Date